Paediatric Sepsis 4

Digital solutions in paediatric sepsis: current state, challenges, and opportunities to improve care around the world

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The digitisation of health care is offering the promise of transforming the management of paediatric sepsis, which is a major source of morbidity and mortality in children worldwide. Digital technology is already making an impact in paediatric sepsis, but is almost exclusively benefiting patients in high-resource health-care settings. However, digital tools can be highly scalable and cost-effective, and—with the right planning—have the potential to reduce global health disparities. Novel digital solutions, from wearable devices and mobile apps, to electronic health record-embedded decision support tools, have an unprecedented opportunity to transform paediatric sepsis research and care. In this Series paper, we describe the current state of digital solutions in paediatric sepsis around the world, the advances in digital technology that are enabling the development of novel applications, and the potential effect of advances in artificial intelligence in paediatric sepsis research and clinical care.

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Introduction

The digitisation of health care around the world is offering unprecedented opportunities to capture and learn from real-world data, democratise medical knowledge, and improve care through digital health tools.[1,2] This digitisation could be particularly impactful in paediatric sepsis, which is a source of substantial public health burden worldwide.[3,4] The COVID-19 pandemic has illustrated the benefits of rapid data collection and deployment of digital solutions, including pragmatic public health and research registries, close to real-time feedback on epidemiological and health-system operational trends, and rapid deployment of randomised control trials (RCTs) embedded in electronic health records (EHRs).[5] Many of these achievements relied on existing digital structures in different health-care institutions and the urgency to enable interoperability across organisations. By contrast, despite the outsized contribution of sepsis to morbidity and mortality globally, research on and clinical care for sepsis remain largely reliant on traditional human-driven approaches, with a shortage of reliable data extraction, standardisation, analysis, or feedback.[6] Furthermore, when it exists, digital technology innovation in sepsis care tends to benefit patients in highly resourced health-care settings, which magnifies the already disproportionate effect sepsis has in low-income and middle-income countries (LMICs) compared with high-income countries.[3,4] Even in highly resourced health-care settings, digital solutions for paediatric sepsis tend to lag behind those for adults. However, strategies leveraging digital solutions can be highly scalable and cost-effective and—if developed, tested, and deployed equitably—have the potential to reduce global disparities in sepsis care.

In this Series paper, we review and discuss: the current state of digital solutions in paediatric sepsis, the state-of-the-art in clinical decision support (CDS) tools, the challenges and opportunities of digital tools in low-resource health-care settings, the promise of data-driven phenotyping to advance precision medicine in paediatric sepsis, the role of digital technology to predict sepsis outcomes, and the future of paediatric sepsis research and clinical care. Health-care professionals who provide care to acutely ill children can use the information in this Series paper to advance their understanding and use of digital solutions for paediatric sepsis in their local context and to help them consider novel applications in the future.

The current state: level of digitisation of paediatric sepsis worldwide and real-world use cases

Digital solutions for paediatric sepsis can be considered across the care continuum, from presentation, to treatment, to long-term follow-up (figure 1)—there are many crucial points where it has been shown that digital solutions can have an important role. For example, precise capture of paediatric sepsis incidence is required to measure burden of disease from an epidemiological standpoint, and to optimise coding and billing in health-care systems. A Global Burden of Disease study showed that more specific estimates of global sepsis incidence can be obtained by combining criteria of infection with those of organ dysfunction.[3] The increasing availability of EHR data, coupled with simple operationalisation of sepsis as infection with life-threatening organ dysfunction, have enabled the development of standardised coding scripts that search routine health-care data for the presence or absence of specific sepsis

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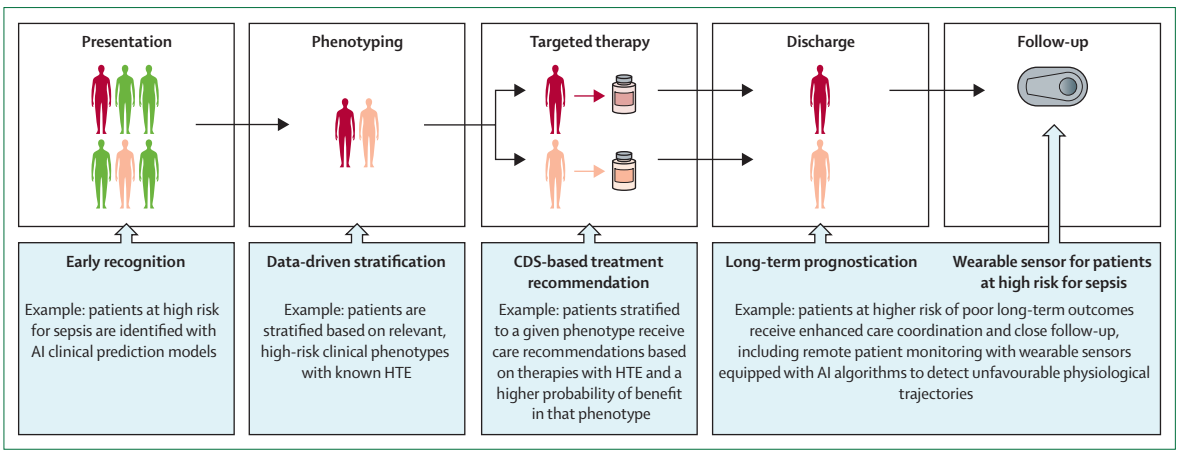

Figure 1: **The digital paediatric sepsis journey**
AI=artificial intelligence. CDS=clinical decision support. HTE=heterogeneity of treatment effect.

criteria in children and adults.[7,8] For children, the Pediatric Sepsis Definition Task Force have developed more generalisable, robust, and better performing criteria than previous paediatric sepsis criteria to screen and diagnose sepsis and septic shock using an EHR-based dataset of over 3·6 million paediatric hospital encounters from both high and low resourced health-care settings.[9,10]

Systematic quality improvement in sepsis care is another area in which digital solutions are becoming increasingly impactful. Pathways, such as Sepsis-6 in the UK, originated as traditional paper-based documents serving as screening tools, cognitive aides, and data collection tools, but many institutions have digitised such content to facilitate access and analysis, with varying degrees of automation in the extraction process.[11,12] The development, dissemination, and implementation of CDS tools in EHRs have also shown their potential in improving the timeliness and quality of care in paediatric sepsis, and have been a main focus of multicentre quality improvement initiatives, such as the Improving Pediatric Sepsis Outcomes collaborative in the USA.[13,14] The main use of CDS tools in EHRs to date has been to enhance early recognition in sepsis screening.[15]

In more sophisticated use cases, digital solutions have leveraged continuous physiological monitoring data, which are widely available in neonatal and paediatric intensive care units (ICUs), to improve the recognition of sepsis. For example, the use of an algorithm based on heart rate characteristics to detect neonatal sepsis earlier than usual care was associated with reduced mortality in an RCT.[16] However, of note, the main body of work of digitisation in sepsis has been done in large academic paediatric institutions in highly resourced health-care settings, and the solutions have had very little spread to low resource health-care settings. Furthermore, even in better-resourced health-care settings, the majority of digital applications in paediatric sepsis are based on static, rule-based decision support as opposed to more dynamic artificial intelligence (AI) models (figure 2).

Clinical decision support systems: use of digital technology to enhance paediatric sepsis recognition and optimise care

CDS tools are designed to enhance clinical decision making and improve quality of care by providing the right information to the right person at the right time. Tools that fall into this broad definition of CDS in paediatric sepsis include clinical guidelines, EHR order sets, alerts and best practice recommendations in EHRs, and data reports or dashboards. Most of the use cases in sepsis, however, have focused on rule-based algorithms used for screening and early recognition of sepsis and subsequent alerting of clinicians, particularly in the emergency department setting, with some examples of machine learning models developed to predict sepsis or septic shock. Although many hospitals informally report using CDS for sepsis screening, few have published their tools, and fewer have published rigorous evaluations of the effects of these tools on sepsis care processes and outcomes in their daily practice. Many tools and prediction models have been proposed or tested in retrospective datasets of children or operate silently in the background of EHRs, but few hospitals have reported on the bedside implementation of these prediction models and CDS tools. In a 2024 scoping review of supervised machine learning models in acutely and critically ill children, 18 studies were identified that focused on the prediction of sepsis or septic shock, but only three of these studies resulted in a model being implemented clinically as a data-driven CDS tool, and only one tool was implemented in more than one hospital.[17] Similarly, a 2022 scoping review of rule-based CDS tools for paediatric sepsis screening identified only seven publications and six conference abstracts that were relevant, but only four

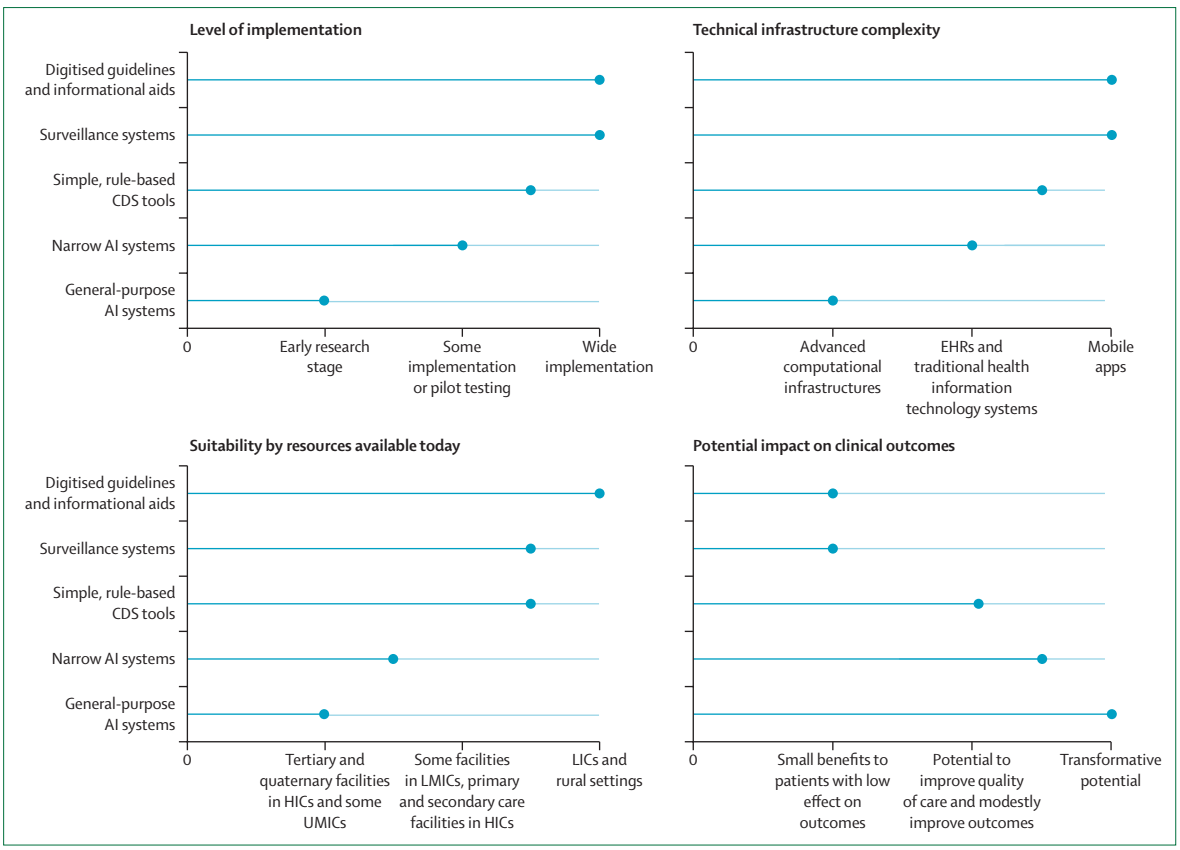

Figure 2: **Level of implementation, complexity, resource-based suitability, and impact of different digital technology solutions in paediatric sepsis**
This figure represents an assessment and illustration of the present and future of the field of digital solutions in paediatric sepsis, performed by the authors, and does not represent a quantitative evaluation of the literature. AI=artificial intelligence. CDS=clinical decision support. EHRs=electronic health records. HICs=high-income countries. LICs=low-income countries. LMICs=low-income and middle-income countries. UMICs=upper-middle-income countries.

described the clinical outcomes associated with implementation of those tools.[18] Eisenberg and colleagues described the development and implementation of a rule-based CDS tool in the emergency department at a single centre, based on the 2005 International Pediatric Sepsis Consensus Conference definitions.[19,20] While the test performance was promising (sensitivity improved from 66% to 85%, and specificity from 91% to 95%, compared with manual review), the study showed no effect on patient care or outcomes. Nonetheless, the clinicians chose to keep the CDS live, suggesting that there could be other benefits to the CDS that are not detectable in the aggregate outcomes measured in the study.[19] Stephen and colleagues found similar results with the implementation of a sepsis prediction model-based CDS tool in a paediatric inpatient setting.[21,22] Having a better understanding of the factors associated with the apparent lack of clinical improvement for some of these CDS tools is crucial. The studies were possibly underpowered, or perhaps these automated tools were being studied in highly resourced academic health-care centres, where measurable improvements from an already good baseline might be harder to achieve.

The patient groups that could benefit or be harmed by CDS tools should be assessed, particularly to identify whether a tool might perpetuate biases or inequities in clinically vulnerable or clinically underserved populations. For example, one CDS tool showed increased compliance with sepsis protocols in all paediatric patients, however it did not change timeliness of care in patients with high-risk conditions (eg, technology-dependent or immunosuppressed), which could possibly reflect that clinicians were adequately detecting sepsis in patients at high risk of developing sepsis before the tool's introduction.[23] Investigators studying the same CDS tool also noted that implementation of CDS for sepsis was associated with fewer discrepancies in the recognition of sepsis when stratified by race.[24] These types of subgroup and follow-up analyses are crucial to understanding the effect these tools could have in real-world scenarios.

Like all prediction models, CDS-based algorithms used for sepsis detection can have varying performance in different settings. In a study of the performance of a proprietary sepsis model for adults developed by a major EHR vendor, investigators found that in nine hospitals

the model had overall poor performance and lower performance in the hospitals with high patient numbers compared with those with low patient numbers, which indicates that the model might not perform as well in the busier hospitals in which it would probably have the biggest potential impact.[25] External validation, consideration for transferability to different settings and local adaptation, and ongoing calibration of prediction models and data-driven algorithms are thus necessary, especially in paediatric institutions, given the variable mix of patient populations with vastly different sepsis risks. In particular, local adaptation could improve clinical performance, but presents challenges from regulatory, governance, human resources, cost, and technical standpoints, and might limit the ability to perform benchmarking across sites. Open source tools and code sharing can support wider and more equitable dissemination of CDS tools, particularly with the use of interoperability standards such as the Fast Healthcare Interoperability Resources.[26]

Applying validated implementation frameworks could improve dissemination approaches through qualitative and quantitative understanding of the effect of CDS on clinical workflows and medical decision making, and degree of adoption and overall clinical effectiveness. Some strategies have been shown to improve end-user acceptability, implementation, and dissemination. For example, iterative testing and revision of CDS tools with end-users in simulated environments, before taking the CDS to broad use in live EHRs, could be conducive to more successful implementations.[27]

Digital tools for sepsis in low resource health-care settings: potential and pitfalls

The possibilites of digital technology use to improve paediatric sepsis care are particularly important in LMICs, which bear the majority of sepsis incidence and mortality, yet have far less health-care resources, staff, and training available.[3] When contextually validated, digital CDS tools offer an evidence-based and patient-centred approach to care that can be used even by minimally trained health-care workers, who are commonplace in many LMICs.[28] Such strategies are increasingly recognised as essential to advancing universal health-care access.[1,29] In many low health-care resource settings, health care is often delivered by a diverse cadre of health-care workers with varying levels of training, and community health workers play a substantial role in health-care delivery. Empowering community health-care workers to use CDS tools that aid in the timely recognition and referral of those with suspected sepsis is crucially important.[30] CDS tools that are well integrated into the clinical workflow can enhance care efficiency while helping better standardise sepsis diagnosis and management, with opportunities for embedded data collection and tracking, which is essential for effective quality improvement initiatives and particularly important in many LMIC settings where health data poverty is a major issue.[14,31,32]

In the past decade, there has been substantial growth in collaborative research networks working on paediatric sepsis and collecting rich clinical datasets in LMICs within Latin America,[33] Africa,[34] and Asia.[35] The datasets generated through these collaborative networks represent important sources for generating local knowledge about paediatric sepsis and a starting point for the development and dissemination of context-sensitive CDS tools.

Although digital platforms and CDS tools hold immense promise, several challenges limit their potential for adoption globally. The LMIC context is highly heterogeneous, varying widely both within and between countries. Marked differences across LMICs and compared with high-income countries (HICs) in the underlying causes of sepsis, as well as key underlying comorbidities, challenge the development of contextually appropriate data-driven tools. A tool to identify children at risk of sepsis in a community setting in Uganda will differ substantially from a tool to identify the same patients in an emergency department setting in Colombia. Furthermore, variations in region-specific resources and priorities make a one-size-fits-all tool improbable, as the use cases and specific needs of sepsis CDS tools vary considerably, with local validation and adaptation posing additional challenges related to data privacy, ownership, and availability. Hence, a useful tool must be adaptable to, and validated within, a variety of settings. These requirements, however, bias the development of such useful tools towards settings with more health-care resources, such as those within HICs.[36]

High heterogeneity in digital maturity at all levels of LMIC health-care systems presents another crucial adoption challenge. Disparities in access and exposure to digital tools among health-care workers contribute to varying levels of digital literacy and enthusiasm for embracing novel health technologies. The integration of digital CDS tools must, therefore, include robust training systems and extensive usability evaluations to fully harness their potential,[36] which is why WHO proposed to develop a digital investment guide focusing on integration aspects of digital health innovations.[37] Furthermore, WHO has also promoted the use of Digital Adaptation Kits in operationalising recommendations and interoperability standards for digital health tools.[37,38] Recognising that digital tools do not operate independently and must be able to be integrated into a wide range of contexts is essential during their design, validation, and implementation phases.[39]

One important potential pathway to scale CDS tool dissemination is by their integration into medical monitoring devices (eg, vital signs monitors). Although the adaptability and cost of medical devices have historically represented major hurdles in LMIC environments, newer initiatives are supporting the development and evaluation of point-of-care devices and

digital tools in these settings.[40] Increasing focus on the development of low-cost, high-quality, clinical monitoring devices has the potential to not only improve clinical care, but also assist in guiding clinical decision making, if validated models and CDS tools are made available to device manufacturers.[41]

With the continued growth of digital health innovations in LMIC settings, where regulation is often weak and poorly developed compared with HICs, governance issues become increasingly challenging, especially for local innovators with limited resources, experience, and investment.[42,43] Overcoming these hurdles necessitates adequate funding, careful planning, meaningful collaborations, rigorous research, and a deep understanding of local contexts.

Data-driven sepsis phenotyping: the potential of scalable precision medicine leveraging digital technology

Heterogeneity is high in the clinical presentation and underlying pathobiology of paediatric sepsis.[44,45] Unravelling this heterogeneity has been identified as a major research priority in the path towards precision medicine in critical care.[46] The identification of more homogeneous subgroups of patients with sepsis—often called phenotypes—has been an area of active study in the past decade. Classification of patients into phenotypes can, in theory, lead to the development of targeted therapies and improved outcomes.[47] Various research groups have taken different approaches to identify and characterise these sepsis phenotypes at the genomic, proteomic, immune cell, organ system, and clinico-physiological levels.[44,45,48,49] Major limitations of more complex approaches, such as those that require genomic or specialised biomarker analyses, are that they could be too complex, too slow, or too expensive for widespread clinical implementation in the near future, particularly in low health-care resource settings (figure 3). Strategies that leverage more widespread tools and data, such as EHRs and routinely collected clinical variables, could potentially have a greater effect in more clinical settings and differently resourced contexts, including community hospital settings, rural areas, and LMICs, where access to advanced biomedical technologies remains scarce.[50] Derivation of phenotypes can be done with various unsupervised machine learning algorithms, including use of clustering at single timepoints,[49,51] or trajectory modelling.[44,50] Validation approaches include assessing the reproducibility of the phenotypes, and their prognostic and therapeutic relevance, including any evidence of heterogeneity of treatment effect.[42]

In a 2021 consensus statement, experts in adult and paediatric critical care from around the world agreed that one of the top priorities in precision medicine in the critical care setting is to develop tools for real-time application of precision medicine approaches, specifically

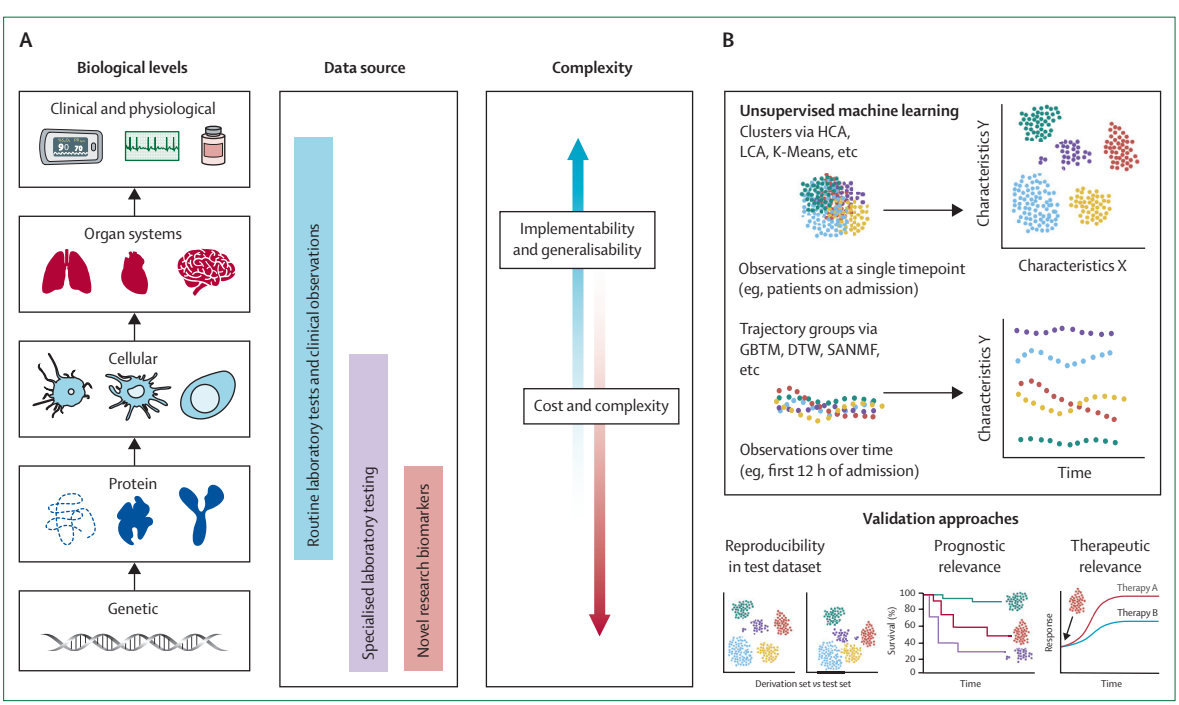

Figure 3: **Data-driven phenotyping approaches and validation**
(A) Data-driven phenotypes of paediatric sepsis have been studied at different biological levels.[44,45,48,49] These biological levels have been studied using various types of data sources and imply different levels of complexity. (B) Various unsupervised machine learning algorithms can be used to derive phenotypes, which can then be validated in different ways. HCA=hierarchical clustering analysis. LCA=latent class analysis. GBTM=group-based trajectory modelling. DTW=dynamic time warping. SANMF=subgraph-augmented non-negative matrix factorisation.

strategies that leverage EHRs and novel digital technologies to improve care.[46] These strategies could include use of real-time clinical and laboratory data to identify patients with sepsis, identifying sepsis subgroups that could benefit from specific interventions using machine learning to identify subgroups, and use of real-time CDS tools to provide treatment recommendations to health-care workers at the bedside.[46] Successful strategies would face a much shorter translational gap than more complex or costly technologies, and have the potential to advance the field of precision medicine in sepsis in the near future.[51,52]

Investigators studying sepsis phenotypes using clinical data and data-driven approaches commonly use unsupervised machine learning algorithms, which are designed to find natural groupings in the data, to derive candidate phenotypes before the candidate phenotypes undergo validation.[2,47] Clinical phenotypes of sepsis derived with these approaches in adult and paediatric patients have shown both prognostic and therapeutic relevance, including heterogeneity of treatment effect (HTE) to common adjuvant therapies. HTE is the non-random variability in the direction and magnitude of treatment effects for individuals or subgroups within a population, and is a hallmark of precision medicine.[53] For example, Seymour and colleagues used EHR data from a large, multicentre cohort of adult patients with sepsis to derive and validate four clinical phenotypes that showed HTE to therapeutic approaches, such as early-goal directed therapy.[54] Bhavani and colleagues derived and validated four phenotypes of sepsis using the trajectories of vital signs in the first 8 h of presentation in 12 473 adults with sepsis in a multicentre study in the same health system, and showed that the groups had a HTE to balanced fluids versus saline fluids.[55] Qin and colleagues derived four phenotypes of paediatric sepsis using routinely collected clinical variables in a multicentre observational cohort of 404 children, and correlated the different phenotypes with distinct biomarker profiles and risk for poor outcomes.[56] Sanchez-Pinto and colleagues derived and validated a sepsis phenotype characterised by persistent hypoxaemia, encephalopathy, and shock, in a multicentre cohort of over 15 000 children with sepsis, and found that it was associated with HTE to both hydrocortisone therapy and albumin infusions.[49] However, these promising findings are tempered by the limitations of observational data and the inability to fully account for all possible confounders. Prospective validation and clinical trials are needed before these types of findings can be translated into routine clinical practice.

Despite the promise of digital technologies enabling phenotype-driven care in paediatric sepsis, to our knowledge, none of these approaches have yet been implemented in real time. Although point-of-care tests for novel biomarker profiles will probably become available in the future,[57] such tools might not be suitable for widespread use and could further exacerbate disparities in care. Thus, low-cost digital technologies need to be developed for real-time clinical profiling that can be deployed globally in an equitable manner. To test the effect of precision medicine approaches in various settings, it will be imperative to develop a robust digital trial infrastructure for children with sepsis around the world, where eligibility screening, consenting, randomisation, treatment recommendations, and outcome determination occur primarily through use of digital tools embedded in EHRs and other digital platforms.[32]

Sepsis outcomes: prediction and prognostication using digital technology

The effects and outcomes of sepsis in children can be devastating, wide-ranging, and long lasting, and can vary substantially on the basis of geography, health-care access, resource availability, underlying health conditions, and other social determinants of health.[30,31,58] Poor outcomes of sepsis in children might occur in both the short term (eg, organ dysfunction and early death) and long term (eg, developmental, learning, and behavioural difficulties, and decreased quality of life). These challenges can continue through adulthood, and can affect employment, social relationships, and broader contributions to society.[59]

Published prediction models and scores variably incorporate clinical, laboratory, and physiological parameters, and novel biomarkers. Short-term prediction models and scores have predominantly focused on predicting early deterioration, mortality, organ dysfunction, and length of hospital stay. Examples of these models and scores assessed in children with sepsis include various versions of paediatric early warning scores,[60] paediatric risk of mortality scores and indices,[61,62] the Pediatric Logistic Organ Dysfunction (PELOD)-2 score,[63] and the pediatric Sequential Organ Failure Assessment score.[64,65] Additionally, the Pediatric Sepsis Biomarker Risk Model (PERSEVERE), developed by Wong and colleagues, uses five biomarkers to predict 28-day all-cause mortality and persistent organ dysfunction in children with septic shock.[66] Despite similarities, paediatric and adult sepsis prediction models differ primarily due to variations in patient age-specific physiological characteristics and comorbidities. Paediatric models often consider growth and development factors, incorporating age-specific cutoffs for vital signs and laboratory values. In this context, it is important to remember that many age-specific thresholds applied to vital data, such as heart rate or blood pressure, are based on historic, relatively small cohorts, and might not necessarily represent contemporary data-driven categories. Conversely, adult prediction models used in sepsis and other related conditions lend more weight to chronic health conditions, coexisting organ dysfunction, and age-independent physiological parameters.[67,68]

Overall, compared with models for short-term outcomes, there is a clear shortage of models predicting long-term outcomes in children, encompassing both health-related quality of life (HRQoL) and functional impairment.

A 2019 study, exploring predictors of HRQoL in 790 paediatric sepsis survivors at a median 31 days post-discharge, found that older age, immunocompromised status, septic shock, and prolonged hospital stay were all associated with reduced HRQoL; however, scoring systems such as PELOD-2 were not associated with worse HRQoL, which indicates that the most commonly used models that predict short-term outcomes might not be effective in predicting long-term outcomes.[69] In a study of a subset of children who had survived community-acquired septic shock in the Life After Pediatric Sepsis Evaluation study, the PERSEVERE biomarker-based model was not predictive of HRQoL level at 3 months after hospitalisation.[70] In a single-centre study published in 2021, those survivors of paediatric septic shock who had lower heart rate variability at discharge and those who had a smaller improvement in heart rate variability from illness to discharge had higher rates of future emergency department visits and hospital readmission, which are associated with lower quality of life.[71] Also, Gilholm and colleagues developed an AI model using discharge data from children discharged from ICU to predict failure to reach minimal school requirements at a median follow-up duration of 6 years across different patient populations, including those who received treatment for sepsis, and found that socioeconomic status, underlying health conditions, and severity of illness were predictive of failure to meet minimal school requirements.[72] Although long-term outcomes are increasingly recognised as a research priority area, most of the published models tend to have small sample sizes, short follow-up duration, and have not been externally validated, and have rarely been implemented for real-world use.[73] Furthermore, the prediction models and scores discussed in this section have largely been developed in HICs and might not be appropriate for use in low resource health-care settings, due to differences in health-care infrastructure, resources, and patient demographics.[74]

Integrating and synthesising large and diverse volumes of data relating to a single patient as inputs to a prediction model can offer individualised risk assessments, facilitating timely interventions and improving clinical decision making, particularly when integrated into real-time monitoring. However, there remains a paucity of literature showing the utility of such approaches in real-world implementations. The development of predictive models that are shown to be useful in real-world settings remains an area of crucial need for further development, particularly as it relates to designing strategies to improve the outcomes of survivors at high risk of poor long-term outcomes.[74]

The future state: leveraging AI to advance the science and care of paediatric patients with sepsis

Although first generation CDS systems and other digital tools for paediatric sepsis have been deployed with various levels of success, the volume of health-care data that has been collected in the past decade is enabling the development of more versatile algorithms and models.[75] Recent advances in AI and health-care technology promise to unlock profound capabilities of digital solutions for paediatric sepsis in the near future. Furthermore, with the rapid growth of models for both adult and paediatric sepsis, there is an opportunity to leverage AI model transferability approaches for models developed in adults or in different paediatric cohorts, to adapt and validate them in paediatric settings (figure 4).

In the past 5 years, the rapid expansion of AI has increasingly been used for coding, billing, hospital management, and to support early recognition of patients whose health status is deteriorating.[76] Traditional AI-based prediction models (often called narrow AI) use large amounts of clinical and operational data to learn how to excel at a single, narrow task, such as predicting sepsis based on historical data.[77] This prediction usually requires the outcome of interest to be labelled by humans, so that the model can learn the mathematical relationship between the predictors and the outcome in order to predict what will happen to a new patient. More recently, large-scale pre-trained AI models—also called foundation models—have been challenging this prevailing framework; they have shown impressive capabilities across various application domains and typically require little labelled data to learn or to adapt to a new task.[75] Only a few years ago, developing a medical AI system required training it from the beginning, which presupposed a substantial effort of collecting and harmonising large-scale patient cohort data. Nowadays, large-scale AI models can be

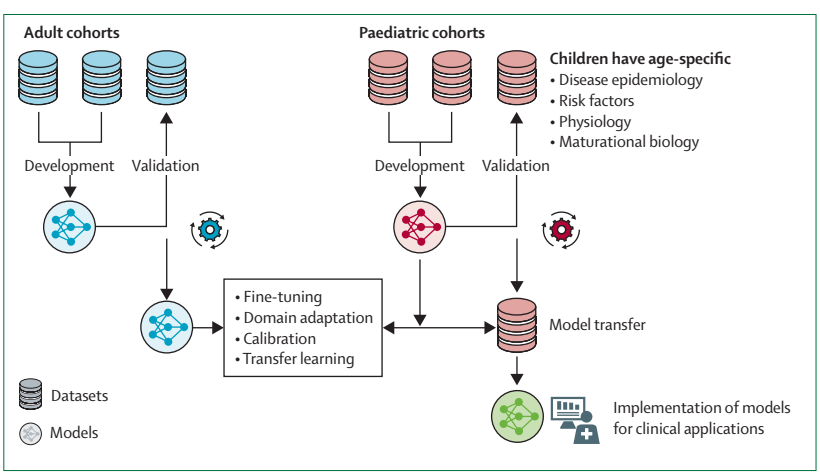

Figure 4: **Framework for transferability of adult sepsis algorithms to paediatric cohorts**
This figure shows initial algorithm development in adult and paediatric cohorts, followed by incorporation of paediatric-specific factors and computational adjustments. We envision that paediatric sepsis algorithms can borrow from the rich knowledge of adult sepsis prediction models derived from large-scale adult cohorts, and those models derived in other paediatric sepsis cohorts. For example, adult cohort models can be adapted to paediatric cohorts with strategies such as transfer learning and domain adaptation, to teach pretrained sepsis algorithms the characteristics of paediatric sepsis. For implementation purposes, transferred models need to be recalibrated on the target paediatric cohort. Likewise, transfer of paediatric sepsis algorithms to adult algorithms is also possible, necessitating recalibration on the target adult cohorts.

	Proposed solutions
Small number of large datasets with adequate representativeness of populations of interest to develop digital tools	Funding efforts to increase quantity and quality of data collection and digitisation of these data in data-poor regions; developing tools, policies, and approaches that facilitate data harmonisation and improve data quality; promoting data sharing initiatives that maximise data interoperability and data utility, while ensuring patient privacy is preserved; creating a culture of data literacy and data-driven discovery
The development of digital tools is costly and often results in restricted effect on patient outcomes	Developing novel digital tools that are cost-effective by using open source code and interoperable platforms that maximise dissemination and allow for context-specific adaptation; developing digital tools using human-centred design and implementation science approaches that optimise the integration of the tools into clinical workflows
Digital tools are often developed and deployed with little or no validation or monitoring	Designing clinical trials and prospective studies that rigorously test the clinical effectiveness, feasibility, acceptability, and sustainability of new digital tools in the various contexts of use for which they are designed or adapted (eg, high and low health-care resource, emergency room and inpatient, pre-hospital and post-discharge), which will be particularly important with the advent of more powerful artificial intelligence-based generalist models; developing frameworks for post-implementation monitoring, ongoing validation, and planned removal of underperforming and ineffective tools
Novel digital tools might be preferentially implemented in high-resource health-care settings and thereby contribute to the global inequities in paediatric sepsis care	Ensuring equitable dissemination and implementation of effective digital solutions by developing global collaborations to share knowledge and expertise, and by funding efforts to develop new cost-effective digital tools or adapt existing tools to settings with different levels of health-care resources that could benefit from digital solutions; aligning digital tool development and digital innovation with the procurement and development of essential human and material resources, and not substituting for those

Table: **Barriers and proposed solutions for the development of digital tools for paediatric sepsis care**

reused as powerful knowledge engines, which could drastically reduce the amount of required patient data for training and offer the opportunity to leverage more of these data for in-depth validations. For instance, large language AI models (eg, generative pre-trained transformer-4, and other comparable models) can be trained on a sizable portion of the entire medical literature.[78] The promise of such models is that they can be easily adapted to new tasks with only few data while allowing for new levels of interactivity, in cases where the model underlies a chatbot interface. Unravelling the full potential of such knowledgeable and ever more general-purpose models could profoundly impact medical practice (figure 2).[79] For example, these models could ingest data from various data sources (eg, clinical notes, imaging, physiological, or laboratory) and make tailored recommendations for treatments or more accurate prognostication on the basis of historical data for similar patients or the latest clinical guidelines.

However, so-called generalist AI models have not been trained on the heterogeneous sets of data that clinicians currently use for decision making, as the datasets are not publicly available; these data include clinical observations, imaging studies, conversations in the form of audio or video materials, test results, and waveforms from physiological sensors. This situation highlights the importance of developing and evaluating foundation models focused on the medical domain.[80] For complex clinical syndromes (eg, sepsis), such models could integrate the vast information flow of patient-level data with relevant biomedical literature to provide a general-purpose aid to clinicians that can analyse these data and provide diagnoses and treatment recommendations. Embedding such models in EHR systems could enable the automatic analysis of patient data and the detection of subtle signs and patterns of sepsis that might be overlooked by clinicians, who are already exposed to information overload, and have inherent cognitive load limitations.[80]

However, AI models have relevant limitations when it comes to clinical applications. Traditional narrow AI models are known to degrade in performance under data distribution shifts, which occur frequently in clinical practice.[81] General-purpose AI systems, such as foundation models, can be more robust in relation to performance degradation, but they are prone to so-called hallucinations (generated statements that are factually incorrect, but might not be immediately recognisable as such by users). The thorough evaluation and validation of these models and the education of clinicians on their appropriate use are, therefore, paramount before real-world implementations are done.

Beyond the boundaries of health-care institutions, digital solutions also have a role to help improve outcomes of paediatric sepsis in patients' homes. Although still immature, the field of remote patient monitoring is evolving rapidly, particularly as technological advancements allow for more efficient and effective monitoring.[82] In the near future, children at high risk of developing sepsis or those recovering from it will probably be equipped with novel sensors and monitored remotely with the aid of AI algorithms (figure 1).[83] Wearable sensors are not only capable of recording cardiorespiratory signals, temperature, and motion, with flexible and unobtrusive materials,[84] but researchers are also developing sensors capable of analysing sweat for biomarkers of disease.[85] The evolution of this technology holds the promise of enabling providers to coordinate care, make earlier diagnoses, and provide targeted treatments at earlier timepoints. One important aspect for this technology will be to ensure that novel sensors are designed specifically for the size, skin, and other characteristics of neonates and children.[41]

The ongoing digital revolution in paediatric sepsis will not be possible without attention to how clinical data are collected, stored, shared, and used. Large-scale data harmonisation across high-resource and low-resource health-care settings are crucial for facilitating collaborative research,[52] guided by the findable, accessible, interoperable, and reusable (FAIR) principles.[86] However, to achieve true data harmonisation and adherence to FAIR principles, substantial challenges must be overcome. These challenges include technical hurdles related to data standardisation and inter-

Search strategy and selection criteria

References for this narrative review were identified through searches of PubMed, Google Scholar, and the authors' expertise in the field. As this Series paper was not a systematic revivew, there were no a priori inclusion and exclusion criteria or set dates for the search, but given the focus on the current state, challenges, and opportunities, articles published in the 5 years before work began on this Series paper (published since 2018) were prioritised, and only publications in English were considered. We used search terms appropriate for each section, specifically "digital health", "electronic health record", "clinical decision support", "phenotypes", "prediction model", "artificial intelligence", and "low and middle income countries" in logical conjunction with the term "sepsis" or "paediatric sepsis". In addition, reference lists from key articles of interest retrieved through the search were searched for additional related publications that the authors deemed important based on their expertise. The final reference list was generated based on originality and relevance to the broad scope of this Series paper.

operability, regulatory concerns about data privacy and security, and the need for international consensus and cooperation for these challenges. Moreover, implementing digital solutions for paediatric sepsis requires overcoming barriers to adoption, such as health-care professionals' digital literacy and established clinical workflows, patients' and families' comfort with advanced technologies, and equitable access to digital tools and infrastructure. A focus on adequate conduct and reporting of trials studying AI-driven CDS tools for paediatric sepsis across different stages of development is also important for transparency and reproducibility.[87] Nevertheless, the new digital era in medicine will continue to be transformative, and clinicians and researchers caring for and studying children with sepsis have a unique opportunity to make substantial progress in addressing the global morbidity and mortality associated with paediatric sepsis with the thoughtful, rigorous, and equitable implementation of AI-driven tools and other digital solutions.

Conclusion

The future of paediatric sepsis care and research is decidedly digital. This journey will require collaboration and innovation, not just in terms of developing the technology, but also in how data collection and data sharing are approached to maximise generalisability and representativeness across differently resourced settings, develop novel digital tools that are cost-effective and easy to implement into existing clinical workflows, design clinical trials and prospective studies that rigorously test the effectiveness of these tools for supporting clinical decision making and are powered to assess their clinical impact, and ensure more equitable dissemination and implementation of effective digital solutions (table). Harnessing the power of digital solutions—from EHR-embedded CDS tools and generalist AI algorithms to wearable devices—gives an unprecedented opportunity to transform paediatric sepsis care and affect the lives of countless children worldwide.

Contributors

LNS-P, LJS, and TDB were responsible for conceptualisation and supervision. LNS-P and TDB were responsible for funding acquisition. LNS-P, MdPAL, KG, HS, MM, RSW, MOW, and LJS wrote the original draft. All authors reviewed and edited the manuscript and approved the final version.

Declaration of interests

RSW served on the data safety monitoring board of the GRACE trial (granulocyte-macrophage colony-stimulating factor for reversal of immunoparalysis in pediatric sepsis-induced multiple organ dysfunction syndrome), chairs the data safety monitoring board of the PRECISE study (personalized immunomodulation in pediatric sepsis-induced multiple organ dysfunction syndrome), and is a co-investigator on the SHIPSS trial (stress hydrocortisone for pediatric septic shock; R01HD096901). LNS-P has stock options in Celldom, Saccharo, Allyx Therapeutics, and InnoSIGN, which are companies focused on diagnostic and therapeutic approaches to cancer and Alzheimer's disease, not sepsis. HS has received support for travel to meetings related to sepsis quality improvement from the Children's Hospital Association, and travel support from the Society of Critical Care Medicine. RSW declares travel support from the Society of Critical Care Medicine, and is co-chair (unpaid) of the Pediatric Sepsis Definitions Task Force for the Society of Critical Care Medicine. LNS-P, HS, LJS, and TDB are members (unpaid) of the Pediatric Sepsis Definitions Task Force for the Society of Critical Care Medicine. All other authors declare no competing interests.

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